

*Conclude*  
*C*  
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*D9*  
*cont*  
Phe-Gln-Glu-Ala-Tyr-Arg-Arg-Phe-Tyr-Gly-Pro-Val) (SEQ ID NO. 44), cortistatin 29 (1-13) (Glp)-Glu-Arg-Pro-Pro-Leu-Gln-Gln-Pro-Pro-His-Arg-Asp) (SEQ ID NO. 45), cortistatin 14 Pro-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Ser-Ser-Cys-Lys; Disulfide bridge: Cys2-Cys13 (SEQ ID NO. 46), PD-145065 (Ac-D-Bhg-Leu-Asp-Ile-Ile-Trp) (SEQ ID NO. 47), PD-142893 (Ac-D-Dip-Leu-Asp-Ile-Ile-Trp) (SEQ ID NO. 48), fibrinogen binding inhibitor peptide (His-His-Leu-Gly-Gly-Ala-Lys-Gln-Ala-Gly-Asp-Val) (SEQ ID NO. 49), leptin (93-105) (Asn-Val-Ile-Gln-Ile-Ser-Asn-Asp-Leu-Glu-Asn-Leu-Arg) (SEQ ID NO. 50), GR 83074 (Boc-Arg-Ala-DTrp-Phe-DPro-Pro-Nle-NH<sub>2</sub>) (SEQ ID NO. 51) Tyr-W-MIF-1 (Tyr-Pro-Trp-Gly-NH<sub>2</sub>) (SEQ ID NO. 52), parathyroid hormone related peptide (107-111) (Thr-Arg-Ser-Ala-Trp) (SEQ ID NO. 53), angiotensinogen (1-14) Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His-Asn (SEQ ID NO. 54), Leupeptin (Ac-Leu-Leu-Arg-CHO); or a modified or truncated fragment thereof.

#### REMARKS

As an initial matter, please change the attorney docket number in this case from "PPT-20479-US" to --55508/45487--.

Claims 1, 6, 9, 10, 21, 23, and 37 have been amended and new claims 52-67 added. Claims 39, 41, 43, 45, 47 and 49 have been canceled without prejudice. The right to file subsequent applications encompassing the canceled subject matter is reserved.

The claim amendments find support throughout the application including the claims as filed originally.

Specific support for language relating to binding between the N terminus of Z peptide and the C terminus of X in claim 1 can be found eg., at pg. 18, line 5 to pg. 19, line 2. See also pg. 19, line 19 to pg. 21, line 11 and the Examples section. See also the Summary of the Invention (disclosing, for instance, peptide conjugates having the covalent binding between Z and X).

Claim 1 has been further amended, and claims 6, 9, 10, 21, 23, and 37 amended, to improve clarity. The amendments are not intended nor should they be construed as bearing on claim patentability.

New claims 52-68 also find support throughout the present application including the claims as filed originally.

New claim 52 has been re-written from claim 1 to include a half-life ratio of at least about 3. Specific support for the new claim as well as dependent claim 53 can be found eg., in claim 1 as filed originally.

New claim 54 has also been re-written from claim 1 to include Z values having about 4 to 10 amino acids. Particular support for that claim as well as dependent claims 55-56 can be found eg., in claim 6 as filed originally.

New claim 57 has been re-written along lines of claim 1 in which Z is at least two or three Lys amino acid units. Specific claim support can be found eg., in claim 9 as filed originally. Dependent claims 58-61 also find particular support in original claim 9.

New claim 62 has been re-written from claim 1 in which Z is  $(\text{Dbu})_n$  or  $(\text{Dpr})_n$ , wherein n is an integer in the range from about 4 to about 10. Dependent claim 63 also finds support in claim 1 as filed originally.

New claim 64 has been re-written from claim 1 in which pharmacologically active peptide sequence (X) consists of at the most about 65 amino acid units. Dependent claim 65 also finds specific support from claim 1 as filed originally.

New claim 66 has been re-written along lines of claim 37 in which the half-life ratio is at least about 3. Dependent claim 67 also finds particular support in claim 37 as filed originally.

New claim 68 combines language from claim 1 (half-life ratio is 2) and claim 16. The new claim 68 further includes language from claim 25 except that in the new claim, reference is made specifically to sequence with a sequence identifier number. New claim 68 finds specific support in claims 1, 16 and 25, for example, as filed originally.

No new matter has been added by virtue of the claim amendments or new claims.

Before turning to the instant office action, it is believed that a brief summary of the invention would be worthwhile.

The invention generally relates to the discovery that by conjugating an active peptide (X) to a stabilizing peptide sequence (Z), it is possible to protect the X peptide from inactivation. Without wishing to be bound to theory, it appears that the Z sequence helps structure the overall peptide conjugate and render the X peptide less randomly shaped. This ordering of the X peptide is believed to help prevent biological inactivation. The invention has a wide spectrum of useful applications including protecting peptides of pharmacological interest from enzymatic degradation.

Turning to the office action, it was stated at pgs. 2-3 that the application contains sequence disclosures that are encompassed by definitions for amino acid sequences provided by 37 CFR 1.821. Specifically, it is alleged that words shown on page 2 of the office action (ie., enkephalin, Leu-enkephalin, ect.) must be accompanied by a sequence listing. Respectfully, Applicant disagrees.

None of the words (enkephalin, Leu-enkephalin, Met-enkephalin, ect.) cited on pg. 2 of the action are "amino acid sequences" under 37 CFR 1.821. Accordingly, no listing should be required. As provided by 37 CFR 1.821:

(a) Nucleotide and/or **amino acid sequences** as used in §§ 1.821 through 1.825 are interpreted to mean an unbranched **sequence** of four or more amino acids or unbranched sequence of ten or more nucleotides. 37 CFR 1.821 (emphases added).

Because none of the cited words including enkephalin, Leu-enkephalin, or Met-enkephalin are "amino acid sequences" under the Rule no sequence listing is needed. See 37 CFR 1.821. Accordingly, reconsideration and withdrawal of the request to include the sequence listing information are requested.

Although Applicant respectfully disagrees with the position that any additional sequence listing information is necessary for consideration of this case, new claim 68 has been added to further prosecution. Specifically, all references in the new claim are accompanied by sequence listing identifiers.

Claim 37 stands rejected on grounds that Applicant has not provided evidence that the claimed method can inhibit neurons from transmitting pain impulses. Applicant respectfully disagrees with the rejection.

It is well established that the standard for determining compliance with the written description requirement of 37 CFR 112, first paragraph, is that the description is of a kind that would allow persons of ordinary skill to recognize that the Applicant invented what is claimed. That is, the Applicant must clearly convey with clarity to those of skill in the field that as of the filing date, he was in possession of the invention claimed. See MPEP §2163.02. A requirement for "evidence" is not part of that standard, either under the USPTO Rules of Practice or the case law. Reconsideration of the rejection in view of the standard set forth under MPEP §2163.02, for example, is respectfully requested.

Applicant's specification, as filed, would allow one of skill in this field to recognize that he invented what is claimed in the method of claim 37. For example, see pg. 6, line 16 to pg. 7, line 14 (disclosing eg., the claimed method of inhibiting particular neuronal impulses). Particular administration regimens are provided at pg. 24, line 3 to pg. 26, line 4, for example.

In view thereof, Applicant has fully complied with the written description requirement of 35 USC §112, first paragraph, and there is no basis for maintaining the instant written description rejection. Thus, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-32, and 37 stand rejected under 35 USC §112, second paragraph as being indefinite. Although Applicant respectfully disagrees, grounds for the rejection have been addressed by this submission.

In particular, claims 1 and 6 have been amended along lines required by the Examiner. More specifically, language removed from claim 6 now appears in new claims 54-56. Related amendments have been made to claims 9, 10, 21, and 23 as requested.

Applicant respectfully disagrees that claim 19 is indefinite. As recited, "Xaa" is defined in the claim as Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Arg, His, Met, Orn, or an amino acid represented by Formula I.

In view thereof, reconsideration and withdrawal of the rejection are requested.

Claims 1-2, 19 and 24 stand rejected under 35 USC §102 as being anticipated by the Neer patent (US Pat. No. 4,833,125). Although Applicant disagrees, basis for the rejection has been addressed by this submission.

In particular claim 1 has been amended to more precisely define position of the Z stabilizing peptide in relation to the X peptide sequence. That is, the **Z peptide is covalently bound by its N terminus to the C-terminus end of the X sequence**. See claim 1 (amended). Importantly, the Z peptide has a carboxy terminus.

In contrast, the cited "Z" sequence from Neer is **within** a PTH polypeptide. See the office action at pp. 5-6. As relied on, the cited "Z" sequence is not bound by its N-terminus to the C-

terminus of any peptide. Also, it has no carboxy terminus. Because the claimed peptide conjugate and the cited PTH polypeptide are different, there can be no anticipation.

Reconsideration and withdrawal of the rejection are respectfully requested.

Claim 1 stands rejected on grounds that it is anticipated by Katz (US Pat. No. 5,716,614) or Ryser (US Pat. No. 4,847,240). Although Applicant disagrees, basis for the rejection has been addressed by this submission.

As relied on, the cited references disclose a polylysine conjugate bound to active peptide. As understood, that binding is not via a Z peptide sequence bound by its N-terminus to the C-terminus of a peptide. See col. 8 of Ryser, for instance (showing binding between a protein carboxy terminus and internal amino group). In contrast, the peptide conjugate of amended claim 1 features Z peptide covalently bound by its N terminus to the C terminus of the X peptide sequence. There is no binding with an internal amino group. Accordingly, there can be no anticipation.

Katz, in particular, is understood to show binding between epsilon groups of a polylysine chain to an agent. See Figure 3 of Katz, for example. That binding does not involve covalent binding between the N-terminus of a Z peptide and the C terminus of an X sequence as featured in amended claim 1.

In view thereof, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-3 stand rejected under 35 USC §102 as being anticipated by Larsen (WO 98/11126). Although Applicants disagree with the rejection, grounds for it have been addressed.

The cited reference has a publication date of 19 March 1998. Applicant has already claimed the benefit of Danish Patent Application No. 0317/98 filed on 9 March 1998 under 35 USC 119. See the Declaration and Power of Attorney signed by Applicant. To support that claim, a

certified copy of the Danish Application was submitted on May 11, 2001. Accordingly, the Larsen reference is not prior art. Withdrawal of the rejection is respectfully requested.

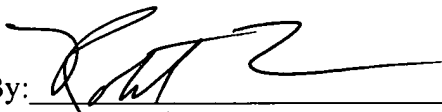
Also submitted on May 11, 2001 is a supplemental Information Disclosure Statement that includes the Huffman reference (US Pat. No. 4,542,124). Consideration of the IDS is requested.

Attached to this submission is a marked-up version of the changes made to the specification and claims. The attached page is captioned "version with markings to show changes made".

It is believed that the application is in condition for allowance, which action is earnestly solicited. Although it is not believed that any fee is needed to consider this submission, the USPTO is authorized to charge our deposit account no. **04-1105** should such fee be deemed necessary.

Respectfully submitted,

Date: June 7, 2004

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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

Claim 1 has been amended as follows:

1. (Amended) A pharmacologically active peptide conjugate having a reduced tendency towards enzymatic cleavage comprising X and Z,

wherein X is a pharmacologically active peptide sequence, and

wherein Z is a stabilising peptide sequence, of 4-20 amino acid units covalently bound by its N terminus to the C terminus end of X wherein each amino acid unit in said stabilising peptide sequence, Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I



wherein R<sup>1</sup> and R<sup>2</sup> are selected from the group consisting of hydrogen, C<sub>1-6</sub>-alkyl, phenyl, and phenyl-methyl, wherein C<sub>1-6</sub>-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R<sup>1</sup> and R<sup>2</sup> together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring, ~~e.g. 2,4-diaminobutanoic acid and 2,3-diaminopropanoic acid;~~ and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence, X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2, ~~preferably at least about 3, such as at least about 5, more preferably at least about 7, such as at least about 9, e.g. at least~~



~~about 10 or when said pharmacologically active peptide X is not orally absorbed, said conjugate is absorbed, ; or a salt thereof.~~

Claim 6 has been amended as follows:

6. (Amended) A peptide conjugate according to claim 1, wherein Z consists of about 4 to about 15 ~~4-15, preferably 4-10, more preferably 4-7, such as 6~~ amino acid units.

Claim 9 has been amended as follows:

9. (Amended) A peptide conjugate according to claim 1, wherein Z comprises at least one Lys amino acid unit ~~, preferably at least two Lys amino acid units, such as at least three Lys amino acid units, e.g. at least four Lys amino acid units, more preferably at least five Lys amino acid units, such as six Lys amino acid units.~~

Claim 10 has been amended as follows:

10. (Amended) A peptide conjugate according to claim 9, wherein Z is (Lys)<sub>n</sub>, wherein n is an integer in the range from about 4 to about 15 ~~4 to 15, preferably in the range from 4 to 10, such as in the range from 4 to 8, e.g. in the range from 4 to 6.~~

Claim 21 has been amended as follows:

21. (Amended) A peptide conjugate according to claim 1, wherein Z is (Dbu)<sub>n</sub> or (Dpr)<sub>n</sub>, wherein n is an integer in the range from about 4 to about 15 ~~4 to 15, preferably in the range from 4 to 10, such as in the range from 4 to 8, e.g. in the range from 4 to 6.~~

Claim 23 has been amended as follows:

23. (Amended) A peptide conjugate according to any one of the preceding claims, wherein said pharmacologically active peptide sequence (X) consists of at the most 75 amino acid units, ~~such as at the most 65, e.g. at the most 60, preferably at the most 55, such as at the most 53, e.g. at the most 50.~~

Claim 37 has been amended as follows:

37. (Amended) A method for inhibiting neurons from transmitting pain impulses to the spinal cord, comprising administering to a subject in need thereof a conjugate comprising enkephalin and a stabilising sequence, Z of 4-20 amino acids covalently attached by its N terminus to the C terminus end of ~~to~~ X, wherein Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I



wherein R<sup>1</sup> and R<sup>2</sup> are selected from the group consisting of hydrogen, C<sub>1-6</sub>-alkyl, phenyl, and phenyl-methyl, wherein C<sub>1-6</sub>-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R<sup>1</sup> and R<sup>2</sup> together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring, ~~e.g. 2,4-diaminobutanoic acid and 2,3-diaminopropanoic acid;~~

wherein the ratio between the half-life of said peptide conjugate and the half-life of enkephalin when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2, ~~preferably at least about 3, such as at least about 5, more preferably at least about 7, such as at least about 9,~~

~~e.g. at least about 10 or when X is not orally absorbed~~ said peptide conjugate is being orally absorbed in an amount effective to inhibit neurons from transmitting pain impulses.

Claims 39, 41, 43, 45, 47 and 49 have been canceled without prejudice.

Kindly add the following new claims 52-67.

52. (New) A pharmacologically active peptide conjugate having a reduced tendency towards enzymatic cleavage comprising X and Z,

wherein X is a pharmacologically active peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bound by its N terminus to the C terminus end of X, wherein each amino acid unit in said stabilising peptide sequence Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I



wherein R<sup>1</sup> and R<sup>2</sup> are selected from the group consisting of hydrogen, C<sub>1-6</sub>-alkyl, phenyl, and phenyl-methyl, wherein C<sub>1-6</sub>-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R<sup>1</sup> and R<sup>2</sup> together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with

carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 3; or a salt thereof.

53. (New) The peptide conjugate of claim 52, wherein the ratio is at least about 5, 7, 9, or 10.

54. (New) A pharmacologically active peptide conjugate having a reduced tendency towards enzymatic cleavage comprising X and Z,

wherein X is a pharmacologically active peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bound by its N terminus to the C terminus end of X, wherein each amino acid unit in said stabilising peptide sequence Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I



wherein R<sup>1</sup> and R<sup>2</sup> are selected from the group consisting of hydrogen, C<sub>1-6</sub>-alkyl, phenyl, and phenyl-methyl, wherein C<sub>1-6</sub>-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R<sup>1</sup> and R<sup>2</sup> together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at

about pH 7.4 at about 37°C or in serum or plasma is at least about 2; or a salt thereof, wherein Z consists of about 4 to about 10 amino acids.

55. (New) The peptide conjugate of claim 54, wherein Z consists of about 4 to about 7 amino acid units.

56. (New) The peptide conjugate of claim 55, wherein Z consists of 6 amino acid units.

57. (New) A pharmacologically active peptide conjugate having a reduced tendency towards enzymatic cleavage comprising X and Z,

wherein X is a pharmacologically active peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bound by its N terminus to the C terminus end of X, wherein each amino acid unit in said stabilising peptide sequence Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I



wherein R<sup>1</sup> and R<sup>2</sup> are selected from the group consisting of hydrogen, C<sub>1-6</sub>-alkyl, phenyl, and phenyl-methyl, wherein C<sub>1-6</sub>-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R<sup>1</sup> and R<sup>2</sup> together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with

carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2; or a salt thereof, wherein Z comprises at least two or three Lys amino acid units.

58. (New) The peptide conjugate of claim 57, wherein Z comprises at least four or five Lys amino acid units.

59. (New) The peptide conjugate of claim 58, wherein Z comprises six Lys amino acid units.

60. (New) The peptide conjugate according to claim 9 or 57, wherein Z is (Lys)<sub>n</sub>, wherein n is an integer in the range from about 4 to 10.

61. (New) The peptide conjugate of claim 9 or 57, wherein Z is (Lys)<sub>n</sub>, wherein n is an integer in the range from about 4 to 8 or about 4 to 6.

62. (New) A pharmacologically active peptide conjugate having a reduced tendency towards enzymatic cleavage comprising X and Z,

wherein X is a pharmacologically active peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bound by its N terminus to the C terminus end of X, wherein each amino acid unit in said stabilising peptide sequence Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I



wherein  $R^1$  and  $R^2$  are selected from the group consisting of hydrogen,  $C_{1-6}$ -alkyl, phenyl, and phenyl-methyl, wherein  $C_{1-6}$ -alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from  $C_{1-6}$ -alkyl,  $C_{2-6}$ -alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or  $R^1$  and  $R^2$  together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2; or a salt thereof, wherein Z is  $(\text{Dbu})_n$  or  $(\text{Dpr})_n$ , wherein n is an integer in the range from about 4 to about 10.

63. (New) The peptide conjugate of claim 62, wherein Z is  $(\text{Dbu})_n$  or  $(\text{Dpr})_n$ , wherein n is an integer such as in the range from 4 to 6.

64. (New) A pharmacologically active peptide conjugate having a reduced tendency towards enzymatic cleavage comprising X and Z,

wherein X is a pharmacologically active peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bound by its N terminus to the C terminus end of X, wherein each amino acid unit in said stabilising peptide sequence Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I



wherein R<sup>1</sup> and R<sup>2</sup> are selected from the group consisting of hydrogen, C<sub>1-6</sub>-alkyl, phenyl, and phenyl-methyl, wherein C<sub>1-6</sub>-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R<sup>1</sup> and R<sup>2</sup> together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2; or a salt thereof, wherein said pharmacologically active peptide sequence (X) consists of at the most about 65 amino acid units.

65. (New) The peptide conjugate of claim 64, wherein said pharmacologically active peptide sequence (X) consists of at the most about 60, about 55, about 53 or about 50 amino acid units.

66. (New) A method for inhibiting neurons from transmitting pain impulses to the spinal cord, comprising administering to a subject in need thereof a conjugate comprising enkephalin and a stabilising sequence, Z of 4-20 amino acids covalently attached to X, wherein Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I



wherein R<sup>1</sup> and R<sup>2</sup> are selected from the group consisting of hydrogen, C<sub>1-6</sub>-alkyl, phenyl, and phenyl-methyl, wherein C<sub>1-6</sub>-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and



phenyl-methyl is optionally substituted with from one to three substituents selected from C<sub>1-6</sub>-alkyl, C<sub>2-6</sub>-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R<sup>1</sup> and R<sup>2</sup> together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring, e.g. 2,4-diaminobutanoic acid and 2,3-diaminopropanoic acid;

wherein the ratio between the half-life of said peptide conjugate and the half-life of enkephalin when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 3, said peptide conjugate being orally absorbed in an amount effective to inhibit neurons from transmitting pain impulses.

67. (New) The method of claim 66, wherein the ratio is at least about 5, about 7, about 9 or about 10.

68. (New) A pharmacologically active peptide conjugate having a reduced tendency towards enzymatic cleavage comprising X and Z,

wherein X is a pharmacologically active peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bound by its N terminus to the C terminus end of X, wherein each amino acid unit in said stabilising peptide sequence Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I



wherein R<sup>1</sup> and R<sup>2</sup> are selected from the group consisting of hydrogen, C<sub>1-6</sub>-alkyl, phenyl, and phenyl-methyl, wherein C<sub>1-6</sub>-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C<sub>1-6</sub>-

alkyl, C<sub>2-6</sub>-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R<sup>1</sup> and R<sup>2</sup> together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring, e.g. 2,4-diaminobutanoic acid and 2,3-diaminopropanoic acid; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least about 2; or a salt thereof, wherein,

Z is Lys<sub>p</sub>-Xaa<sub>q</sub> or Xaa<sub>p</sub>-Lys<sub>q</sub>, wherein p and q are integers in the range from 1 to 14, with the proviso that p+q is in the range of 3-15, and each Xaa is independently selected from the group consisting of Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Arg, His, Orn, 2,4-diaminobutanoic acid, 2,3-diaminopropanoic acid and Met, and further wherein,

X is selected from the group consisting of AF 12505 (Ile-Glu-Gly-Pro-Thr-Leu-Arg-Gln-Trp-Leu-Ala-Ala-Arg-Ala) (SEQ ID NO. 14), insulin-like growth factor I (57-70) (Ala-Leu-Leu-Glu-Thr-Tyr-Cys-Ala-Thr-Pro-Ala-Lys-Ser-Glu) (SEQ ID NO. 15), insulin-like growth factor I (30-41) (Gly-Tyr-Gly-Ser-Ser-Ser-Arg-Arg-Ala-Pro-Gln-Thr) (SEQ ID NO. 16), insulin-like growth factor I (24-41) (Tyr-Phe-Asn-Lys-Pro-Thr-Gly-Tyr-Gly-Ser-Ser-Ser-Arg-Arg-Ala-Pro-Gln-Thr) (SEQ ID NO. 17), insulin-like growth factor II (33-40) (Ser-Arg-Val-Ser-Arg-Arg-Ser-Arg) (SEQ ID NO. 18), insulin-like growth factor II (33-40) (Tyr-Ser-Arg-Val-Ser-Arg-Arg-Ser-Arg) (SEQ ID NO. 19), insulin-like growth factor II (69-84) (Asp-Val-Ser-Thr-Pro-Pro-Thr-Val-Leu-Pro-Asp-Asn-Phe-Pro-Arg-Tyr) (SEQ ID NO. 20), growth hormone (GH)-releasing peptide-6 (GHRP-6) (His-DTrp-Ala-Trp-DPhe-Lys-NH<sub>2</sub>) (SEQ ID NO. 21), beta-Interleukin I (163-171) (Val-Gln-Gly-Glu-Glu-Ser-Asn-Asp-Lys) (SEQ ID NO. 22), beta-Interleukin II (44-56) (Ile-Leu-Asn-Gly-Ile-Asn-Asn-Tyr-Lys-Asn-Pro-Lys-Leu) (SEQ ID NO. 23), Interleukin II (60-70) (Leu-Thr-Phe-Lys-Phe-Tyr-Met-Pro-Lys-Lys-Ala) (SEQ ID NO. 24), exendin-4 (GLP-1 analog) (His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH<sub>2</sub>) (SEQ ID NO. 25), exendin-3 (GLP-1 analog) (His-Ser-Asp-Gly-Thr-Phe-Thr-

Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser) (SEQ ID NO. 26), epidermal growth factor (20-31) Cys(Acm)-Met-His-Ile-Glu-Ser-Leu-Asp-Ser-Tyr-Thr-Cys(Acm) (SEQ ID NO. 27), bivalirudin (Hirulog) (D-Phe-Pro-Arg-Pro-(Gly)<sup>4</sup>-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu) (SEQ ID NO. 28), hirulog-1 D-Phe-Pro-Arg-Pro-(Gly)<sup>4</sup>-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Tyr-Leu (SEQ ID NO. 29), C-type natriuretic peptide (1-53) (CNP) (Asp-Leu-Arg-Val-Asp-Thr-Lys-Ser-Arg-Ala-Ala-Trp-Ala-Arg-Leu-Leu-Gln-Glu-His-Pro-Asn-Ala-Arg-Lys-Tyr-Lys-Gly-Ala-Asn-Lys-Lys-Gly-Leu-Ser-Lys-Gly-Cys-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-Gly-Ser-Met-Ser-Gly-Leu-Gly-Cys; Disulfide bridge: Cys37-Cys53) (SEQ ID NO. 30), "Mini ANP" (Met-Cys-His-cyclohexylAla-Gly-Gly-Arg-Met-Asp-Arg-Ile-Ser-Cys-Tyr-Arg, disulfide bridge cys2-cys13) (SEQ ID NO. 31), Melanotan-II (MT-II, alpha-MSH4-10-NH<sub>2</sub>, or Ac-Nle4-Asp5-His6-D-Phe7-Arg8-Trp9-Lys10) (SEQ ID NO. 32), thymosin alpha1 (TA1) (Ac-Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glu-Ile-Thr-Thr-Lys-Asp-Leu-Lys-Glu-Lys-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn) (SEQ ID NO. 33), Cys-Phe-Ile-Gln-Asn-Cys-Pro-Orn-Gly-NH<sub>2</sub>, Disulfide bridge: Cys1-Cys6) (SEQ ID NO. 34), octreotide (201-995) (DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol; disulfide bridge: Cys2-Cys7) (SEQ ID NO. 35), calcitonin gene-related peptide (CGRP) (Ala-Cys-Asp-Thr-Ala-Thr-Cys-Val-Thr-His-Arg-Leu-Ala-Gly-Leu-Leu-Ser-Arg-Ser-Gly-Gly-Val-Val-Lys-Asn-Asn-Phe-Val-Pro-Thr-Asn-Val-Gly-Ser-Lys-Ala-Phe-NH<sub>2</sub>; Disulfide bridge: Cys2-Cys7) (SEQ ID NO. 36), endomorphin-1 Tyr-Pro-Trp-Phe-NH<sub>2</sub> (SEQ ID NO. 37); endomorphin-2 Tyr-Pro-Phe-Phe-NH<sub>2</sub> (SEQ ID NO. 38), nociceptin (also known as Orphanin FQ, Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln) (SEQ ID NO. 39), angiotensinogen (1-13) (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His) (SEQ ID NO. 40), adrenomodullin (1-12) (Tyr-Arg-Gln-Ser-Met-Asn-Asn-Phe-Gln-Gly-Leu-Arg) (SEQ ID NO. 41), antiarrhythmic peptide (AAP) (Gly-Pro-Hyp-Gly-Ala-Gly) (SEQ ID NO. 42), Antagonist G (Arg-DTrp-(nMe)Phe-DTrp-Leu-Met-NH<sub>2</sub>), indolicidin (Ile-Leu-Pro-Trp-Lys-Trp-Pro-Trp-Trp-Pro-Trp-Arg-Arg-NH<sub>2</sub>) (SEQ ID NO. 43), osteocalcin (37-49) (Gly-Phe-Gln-Glu-Ala-Tyr-Arg-Arg-Phe-Tyr-Gly-Pro-Val) (SEQ ID NO. 44), cortistatin 29 (1-13) (Glp)-Glu-Arg-Pro-Pro-Leu-Gln-Gln-Pro-Pro-His-Arg-Asp) (SEQ ID NO. 45), cortistatin 14 Pro-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Ser-Ser-Cys-Lys; Disulfide bridge: Cys2-Cys13 (SEQ ID NO. 46), PD-145065 (Ac-D-Bhg-Leu-Asp-Ile-Ile-Trp) (SEQ ID NO. 47), PD-142893

(Ac-D-Dip-Leu-Asp-Ile-Ile-Trp) (SEQ ID NO. 48), fibrinogen binding inhibitor peptide (His-His-Leu-Gly-Gly-Ala-Lys-Gln-Ala-Gly-Asp-Val) (SEQ ID NO. 49), leptin (93-105) (Asn-Val-Ile-Gln-Ile-Ser-Asn-Asp-Leu-Glu-Asn-Leu-Arg) (SEQ ID NO. 50), GR 83074 (Boc-Arg-Ala-DTrp-Phe-DPro-Pro-Nle-NH<sub>2</sub>) (SEQ ID NO. 51) Tyr-W-MIF-1 (Tyr-Pro-Trp-Gly-NH<sub>2</sub>) (SEQ ID NO. 52), parathyroid hormone related peptide (107-111) (Thr-Arg-Ser-Ala-Trp) (SEQ ID NO. 53), angiotensinogen (1-14) Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His-Asn (SEQ ID NO. 54), Leupeptin (Ac-Leu-Leu-Arg-CHO); or a modified or truncated fragment thereof.

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